



SHORT COMMUNICATION

A rare case of acute pancreatitis and life-threatening hemolytic anemia associated with Epstein–Barr virus infection in a young healthy adult



Sukhchain Singh^{a,b,*}, Pam Khosla^{b,c}

^a Department of Hospital Medicine at Ingalls Memorial Hospital, Harvey, IL, United States

^b Department of Hematology & Oncology at Mount Sinai Hospital Medical Center, Chicago, IL, United States

^c Department of Hematology & Oncology at Rosalind Franklin University of Medicine and Science, North Chicago, IL, United States

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Summary Epstein–Barr virus (EBV) is a common infection that affects 95% of adults worldwide at some point during life. It is usually asymptomatic or causes a self-limiting clinical syndrome known as infectious mononucleosis. It rarely causes complications. Here, we present a case of a healthy 21-year-old female college student who suffered from severe pancreatitis and life-threatening autoimmune hemolytic anemia in association with EBV infection, and we also discuss the common presentation of EBV infection and the diagnosis and treatment of simple and complicated EBV infection.

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Background

EBV infection is common and affects more than 95% of adults worldwide at some point during life. The clinical syndrome associated with EBV is known as infectious mononucleosis and commonly presents with fever, pharyngitis and lymphadenopathy [1]. EBV infection rarely causes infectious

* Corresponding author at: Division of Hospital Medicine, 4th Floor #422, Ingalls Memorial Hospital, 1 Ingalls Drive, Harvey, IL, United States. Tel.: +1 708 915 4576; fax: +1 708 915 4507.

E-mail address: s.singhmd@outlook.com (S. Singh).

mononucleosis if the primary infection is acquired in childhood. However, more than 30% of adolescents and adults with primary EBV infection develop infectious mononucleosis [2], which is characterized initially by sore-throat-like symptoms that are often followed by palatal petechiae, transaminitis, thrombocytopenia, splenomegaly, and hepatomegaly [1,2]. It usually resolves over a period of weeks or months with no sequelae; however, it can occasionally be complicated by a wide variety of neurologic, hematologic, hepatic, respiratory, and psychological complications [3]. Infectious mononucleosis commonly occurs in children, young adults and persons who live in densely populated buildings, such as dorms [2]. Immunocompromised patients have a high risk of developing infectious mononucleosis. EBV carriers shed virus particles from their salivary glands throughout life, but the rate of shedding is highest during the first year following primary infection [2]. EBV spreads via bodily fluids, most commonly through direct contact with saliva. Although intimate sexual contact is most commonly associated with EBV infection in young adults, it can be transmitted through casual contact, such as a handshake; sharing towels, toothbrushes, food or utensils; and general proximity, with a carrier or infected individual.

Case report

A 21-year-old female college student with a history of migraine presented with complaints of malaise, fever, epigastric pain radiating to the back, nausea, vomiting and sore throat that had been present for three days prior to admission. The patient denied prior exposure to hazardous chemicals, unexpected weight loss, hemorrhagic or thrombotic events, visual disturbance, neurological symptoms, skin rash, high risk sexual behavior and intravenous drug use. She admitted to occasional drinking; however, her last drink was 10 days prior to admission. The patient reported regular menstrual periods lasting from 2 to 3 days without excessive bleeding. One of the patient's siblings reported symptoms consistent with upper respiratory tract infection two weeks prior to the patient's admission. The patient denied intimate contact with any companion in her recent past. Her initial physical examination revealed no toxicity, female appearance, temperature of 99°F, blood pressure of 110/65 mmHg, a mildly injected pharynx, small bilateral shoddy non-tender cervical lymph nodes, and abdominal tenderness in the right upper quadrant and epigastrium.

Laboratory data revealed a total white blood cell count of 7.9 cells/ μ L (70% neutrophils, 7%

atypical lymphocytes), hemoglobin of 3.8 g/dL, platelet count of 157 k/ μ L, aspartate aminotransferase of 98 U/L, alanine aminotransferase of 82 U/L, total bilirubin of 2.4 mg/dL, and lipase of 4301 U/L. Computerized tomography of the abdomen revealed findings consistent with acute pancreatitis, namely pancreatic edema, peripancreatic stranding, periportal lucency with mild pericholecystic edema and mild splenomegaly.

The disease included in the differential diagnosis of anemia were intravascular hemolysis, microangiopathic hemolytic anemia due to disseminated intravascular coagulation (DIC), anemia cause by acute and chronic blood loss resulting from peptic ulcers and possible menorrhagia. Although the patient did not report a history of excessive menstrual blood loss, menorrhagia was included in the differential diagnoses due her age. Acute and chronic blood loss and DIC were ruled out based on the laboratory studies and the patient's history and physical examination. The laboratory studies revealed evidence of acute intravascular hemolysis. The peripheral blood smear demonstrated mild thrombocytopenia marked by anemia with anisocytosis and reticulocytosis. The serological studies (Table 1) revealed acute EBV infection, which could be associated with multi-system involvement in this patient.

The patient's acute autoimmune hemolytic anemia (AIHA) was treated with 1 mg/kg prednisone pulse therapy for five days, and the dose was then tapered over the following two weeks. She also required blood transfusions during the initial phase of hospitalization. The pulse steroid therapy halted the hemolysis, as indicated by stabilization of hemoglobin, increased haptoglobin and normalization of bilirubin by discharge on the 9th day of hospitalization. Her hemoglobin was 9.2 g/dL on day 7 and 9.4 g/dL on day 9 of hospitalization. At the three week outpatient follow-up appointment, her hemoglobin was 10.2 g/dL. Pancreatitis was also successfully treated with conservative management. As her abdominal symptoms completely resolved and her lipase level gradually decreased over the period of hospitalization, radiological confirmation of pancreatic inflammation resolution was deemed unnecessary. The patient made a full recovery with no sequelae.

Discussion

In this case, the diagnosis of infectious mononucleosis was based on the patient's history and physical and laboratory findings. The patient was positive for EBV-IgM antibody and negative for

Table 1 Summary of serological studies.

| Test | Results |
|---------------------------------------|----------------------------|
| Heterophile antibody (Monospot) | Positive |
| EBV-IgM antibody | 3 (>1.1 = acute infection) |
| EBV-IgG antibody | Positive |
| Acute hepatitis A, B & C serology | Negative |
| HIV-1 & 2 antibody | Non-reactive |
| Flow cytometry | No PNH clone |
| Parvovirus-B19 IgM | Negative |
| Parvovirus-B19 IgG | Positive |
| Parvovirus-B19 PCR | Not detected |
| Mycoplasma-IgM/IgG | Negative |
| ANA screen | Negative |
| Anti-smooth muscle IgG antibody | Negative |
| Alpha-1 Antitrypsin | Negative |
| Tissue transglutaminase antibody | Negative |
| Ceruloplasmin | Negative |
| Direct antiglobin test (Coomb's test) | Positive |
| Respiratory viral panel ^a | Negative |
| Cytomegalovirus IgM/IgG | Negative |

EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; Ig, immunoglobulin; PCR, polymerase chain reaction; PNH, paroxysmal nocturnal hematuria.

^a Tested viruses (PCR) include Influenza A, Influenza A subtype H1, Influenza A subtype H3, Influenza B, Respiratory Syncytial Virus, Human Metapneumovirus, Rhinovirus, and Adenovirus.

EBV-IgG antibody. She lacked any other relevant infections, including human immunodeficiency virus (Table 1). According to the American College of Gastroenterology guidelines, the presence of two of the following three characteristics is sufficient for the diagnosis of acute pancreatitis: (1) abdominal pain, (2) serum lipase level higher than three times the upper normal limit, and (3) radiological evidence of acute pancreatitis [4]. The patient had all three of these characteristics, with a serum lipase level more than 10 times the upper normal limit. Therefore, further testing was not necessary to confirm the diagnosis of acute pancreatitis. The source of the patient's infection was unclear. Her sibling, who had a recent self-limiting upper respiratory infection, was considered a potential source. EBV can be transmitted through casual contact, such as a handshake; sharing towels, toothbrushes, food or utensils; and general proximity, with an infected or carrier individual. Unreported exposure of the patient to EBV at her college was also considered but could not be confirmed. Primary EBV

infection is common among college students in the United States. A monthly serological surveillance study revealed that EBV developed in more than 12% of initially seronegative students over the course of three years [5].

EBV is diagnosed based on patient history and physical and laboratory studies. The presence of more than 10% atypical lymphocytes on peripheral blood film helps narrow the differential diagnosis to EBV infection with 75% sensitivity and 92% specificity [6]. Monospot heterophile antibody tests highly specific for EBV, with nearly 100% specificity. It is mainly used to confirm EBV infection because its low sensitivity makes it unsuitable as screening test [6]. Clinicians should be highly suspicious of human immunodeficiency virus infection in patients being examined for possible EBV infection because human immunodeficiency virus can present with similar symptoms to those of EBV and results in a positive Monospot test due to cross-reactivity of EBV antibodies with human immunodeficiency virus antibodies [7]. The possibility of human immunodeficiency virus infection is also important because congenital and acquired immune suppression are important risk factors for EBV infection. Immunosuppressive therapy for a variety of conditions predisposes patients to EBV infection [8]. Polymerase chain reaction can be used to confirm EBV infection if other tests are equivocal or a false positive test result is suspected [6]. Our patient was negative for human immunodeficiency virus.

Acute EBV infection causes AIHA in approximately 3% of patients [3]. Acute pancreatitis associated with EBV is even rarer. Only nine case reports of acute pancreatitis associated with EBV have been reported in the literature [9–11], and most of those cases were reported in children or adolescents [9]. We could not locate any case report in the PubMed database of EBV infection associated with both AIHA and acute pancreatitis in a healthy adult. Our patient was a previously healthy young female who presented with the very rare combination of AIHA and acute pancreatitis.

EBV infection is treated with supportive care; however, corticosteroids decrease the duration and severity of complications, such as airway obstruction, immune-mediated anemia and thrombocytopenia. A trial of corticosteroids may be helpful for patients experiencing life-threatening complications [3,6]. For our patient, a five-day high-dose pulse corticosteroid therapy followed by a two week taper resulted in complete recovery. However, there is insufficient evidence to support the use of corticosteroids for symptom control in cases of uncomplicated infection [6]. Empirical evidence from case reports and small

case series suggest that acyclovir or ganciclovir could be beneficial in the treatment of complicated infections [3,6]. Our patient responded well to the corticosteroid therapy; therefore, we did not administer antiviral treatment. Our main goal was to control hemolysis. Corticosteroids are the drug of choice for the treatment of acute AIHA, regardless of its etiology [12]. Therefore, it is unclear if steroid therapy had any role in controlling the EBV infection in our patient.

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Conflict of interest

None declared.

Ethical approval

Not required.

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References

- [1] Grose C. The many faces of infectious mononucleosis: the spectrum of Epstein–Barr virus infection in children. *Pediatr Rev* 1985;7:35–44.
- [2] Luzuriaga K, Sullivan JL. Infectious mononucleosis. *N Engl J Med* 2010;362:1993–2000.
- [3] Jenson HB. Acute complications of Epstein–Barr virus infectious mononucleosis. *Curr Opin Pediatr* 2000;12:263–8.
- [4] Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013;108(September (9)):1400–15.
- [5] Balfour Jr HH, Odumade OA, Schmeling DO, Mullan BD, Ed JA, Jennifer A. Behavioral, virologic, and immunologic factors associated with acquisition and severity of primary Epstein–Barr virus infection in university students. *J Infect Dis* 2013;207(January (1)):80–8.
- [6] Vouloumanou EK, Rafailidis PI, Falagas ME. Current diagnosis and management of infectious mononucleosis. *Curr Opin Hematol* 2012;19:14–20.
- [7] Walensky RP, Rosenberg ES, Ferraro MJ, Losina E, Walker BD, Freedberg KA. Investigation of primary human immunodeficiency virus infection in patients who test positive for heterophile antibody. *Clin Infect Dis* 2001;33:570–2.
- [8] Bargallo A, Carrion S, Domenech E, Arevalo JA, Manosa, Cabre E, et al. Infectious mononucleosis in patients with inflammatory bowel disease under treatment with azathioprine. *Gastroenterol Hepatol* 2008;31(5):289–92.
- [9] Khawcharoenporn T, Lau WK, Chokrungrvaranon N. Epstein–Barr virus infection with acute pancreatitis. *Int J Infect Dis* 2008;12(March (2)):227–9.
- [10] Marín García D, Ruiz Serrato A, Reina González AM, García Ordóñez MA. Pancreatitis aguda asociada a infección por el virus de EpsteinBarr. *Semergen* 2012;38:476–7.
- [11] López-Ibáñez MC, Moreno-Conde M, Gallego-De-la-Sacristana-López-Serrano Á, García-Catalán-Gallego F, Villar-Ráez A. Acute pancreatitis as atypical manifestation of Epstein–Barr virus infection. *Rev Esp Enferm Dig* 2013;105(August (7)):437–8.
- [12] Zanella A, Barcellini W. Treatment of autoimmune hemolytic anemias. *Haematologica* 2014;99(October (10)):1547–54.

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